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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,495	04/24/2006	Nicolas Mermod	3024-119	1575
<div>46/02 7590 09/09/2011</div> <div>JOYCE VON NATZMER</div> <div>PIQUIGNOT + MYERS LLC</div> <div>200 Madison Avenue</div> <div>Suite 1901</div> <div>New York, NY 10016</div>				
EXAMINER				
QIAN, CELINE X				
ART UNIT		PAPER NUMBER		
1636				
MAIL DATE		DELIVERY MODE		
09/09/2011		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/595,495

Applicant(s)

MERMOD ET AL.

Examiner

CELINE QIAN

Art Unit

1636

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 June 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 5a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 65,67,68,70-72,74-91,103,105-107,111-115,117-119 and 122-126 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 24 April 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-946)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 0611
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: ____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____

Continuation of Disposition of Claims: Claims pending in the application are 15-17,23,24,26,28,34,42-45,48,49,51,55,62-65,67-72,74-93,97-99,103,105-108,110-115,117-119 and 122-126.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 15-17,23,24,26,28,34,42-45,48,49,51,55,62-64,69,92,93,97-100,108 and 110.

DETAILED ACTION

Claims 15-17, 23, 24, 26, 28, 34, 42-45, 48, 49, 51, 55, 62-65, 67-72, 74-93, 97-99, 103, 105-108, 110-115, 117-119 and 122-126 are pending in the application. Claims 15-17, 23, 24, 26, 28, 34, 42-45, 48, 49, 51, 55, 62-64, 69, 92, 93, 97-100, 108, 110 are withdrawn from consideration. Claims 65, 67, 68, 70-72, 74-91, 103, 105-107, 111-115, 117-119 and 122-126 are currently under examination.

This Office Action is in response to the amendment filed on 6/27/2011.

All rejections not reiterated in this office action have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65, 67, 68, 70-72, 74-91, 103, 105-107, 111-115, 117-119 and 122-126 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection has been re-written to address the amendment.**

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: “*specification* shall contain a written description of the invention. . . [emphasis added].” The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that

Art Unit: 1636

“as of the filing date sought, [the inventor] was in possession of the invention.” See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

Applicant may show that he is in “possession” of the invention claimed by describing the invention with all of its claimed limitations “by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention.” See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. Claim 65 recites “a purified and isolated DNA sequence that comprises at least one bent DNA element comprising at least 33% of the TA and/or 33% AT on a stretch of 100 base pairs, and at least one binding site for a DNA binding protein, wherein said purified and isolated DNA sequence is a MAR sequence having at least 90% identity with SEQ ID NO: 25.” The claimed invention encompasses a large genus of nucleic acid sequences having $\geq 90\%$ homology with SEQ ID NO: 25. Since SEQ ID NO: 25 consists 3616 base pair nucleotides, a sequence having 90% homology may contain at least 361 mutations within any position of the nucleotide sequence. The specification discloses identification of MAR sequences which may increase protein expression in CHO cells through bioinformatics computational algorithms. The specification discloses 4 sequences (1-68, 1-6, 1-42 and X-S29) picked out from such potential MARs which displays protein production increasing activity greater than that of the 5' chicken

Art Unit: 1636

lysozyme MAR when linked to the expression construct in CHO cells. The specification discloses all these sequences have a high AT/TA value (mean about 35%, see Table 6) and comprises potential transcription factor binding sites. However, the specification does not disclose whether any sequence with 33% TA and/or 33% AT on a stretch of 100 base pairs and any type of DNA binding site would have protein producing increasing activity in any setting (*in vitro*, *in vivo* or in transgenic organism). The specification does not describe any nucleotide sequences having 90% homology with SEQ ID NO: 25 still possess MAR activity. The specification also fails to teach specific regions within SEQ ID NO: 25 that are responsible for the claimed MAR function.

The information within the prior art at the time of filing does not make up for the deficiency in the specification for describing the structural element that is linked to the claimed function. The specification indeed states in the background section "no clear cut MAR consensus sequence has been found...(page 2, line 37)" and "the identification of MAR by biochemical studies is a long and unpredictable process, various results can be obtained depending on the assay (see page 2, lines 46-47)." With regard to predicting MAR sequence by *in silico* method, the specification teaches all available tools are limited by factors such as poor specificity, the lack of confirmation of large amount of hypothetical MARs identified by such tool, and thus, many of such tools becomes useless to identify potent genetic elements with regard to efficient increasing recombinant protein production (see page 3, 1st-3rd paragraph). Girod et al., published in 2007 (see IDS), 4 years after the date of filing of the present application, state "only a few MARs have been conclusively identified from an estimated number of 50,000 or more per genome." Girod et al. further teach that "although the nuclear matrix binding function of MARs is

Art Unit: 1636

conserved from plants to mammals, their DNA sequence is highly polymorphic, and their activities could not be ascribed to any simple DNA motif. Thus, MAR function has often been related to structural properties rather than to its primary sequence, such as the high DNA strand unwinding and unpairing susceptibility of A+T rich sequences and a high potential for denaturation of the double helix. Whether these features contribute to the transcriptional activity of MARs is yet unknown." Girod et al. then teaches a method of identifying MAR sequences based on the prediction of active MAR sequences have a high potential to accommodate curvature, a deep DNA major groove and a wide minor groove, a weak correlation with DNA melting temperature and the presence of certain transcription factors such as SATB1, NMP4 and homeobox proteins (see page 748, 2nd col., and page 749). Girod et al. disclose that 1,566 sequences from the human genome were identified using above parameter at stringent condition (see page 749, bridging paragraph). Girod et al. disclose that none of the 1,566 sequence can be completely aligned on the mouse genome, and suggesting different primary sequence may contribute to species specificities. Girod et al. further selected several putative MAR sequences based on the basis of their high computed score, location near known ubiquitously expressed genes (to avoid tissue specific activity), and have core elements of various length and/or enriched in various combination of potential transcription factor binding sites (see page 749, last paragraph of col.2). Girod et al. disclose that 6 out of 7 such sequences increased expression of a reporter in stably transfected polyclonal CHO cells substantially. Girod et al. disclose that one of the non-activator, 1-15, does not exhibit obvious difference between active and inactive sequences, wherein it also has highly enriched AT and TA dinucleotides (70%), and no qualitative or quantitative difference

Art Unit: 1636

between core sequences of functional and inactive sequences. Girod et al. assert that the mere presence of an (A+T) rich core elements does not suffice to activate gene expression, and the lack of activity may result from the lack of tissue specific activities in CHO and/or from the requirement of additional DNA features (page 750, 2nd col., 2nd paragraph). Girod et al. suggest that gene activation by MARs may rely on the positioning of a nucleosome in the vicinity of transcription factor binding sites, whereas DNA curvature motif alone is not sufficient for transcriptional activity (see page 752, 1st col., 1st paragraph). Girod et al. acknowledges that MARs display a bewildering array of activities that have been difficult to ascribe to any specific DNA motif (see page 751, 2nd col., 1st sentence of last paragraph).

In view of the teaching in the prior art, it appears that there is no consensus agreement that any of the specific DNA motif may be ascribe to various activities of MARs, especially the protein expression enhancing activity. As such, whether a DNA sequence comprising one bent element comprising at least 33% of the dinucleotide TA and/or at least 33% of the dinucleotide AT on a stretch of 100 contiguous base pairs; and at least one binding site for any type of DNA binding protein, wherein the nucleic acid sequence having 90% homology with SEQ ID NO: 25 can increase protein production is unpredictable. The specification discloses only 4 (4 out of more than one thousand that selected by the computer program) nucleic acids that increase protein production in CHO cells. It appears that the other three sequences having high protein producing activity does not have 90% homology with SEQ ID NO: 25. The specification thus fails to describe a representative of species of nucleic acids having the structural properties comprising at least 33% of the dinucleotide TA and/or at least 33% of the dinucleotide AT

Art Unit: 1636

on a stretch of 100 contiguous base pairs; and at least one binding site for any type of DNA binding protein, and 90% homology with SEQ ID NO: 25, that can have the functional property of increasing protein production in any system. Moreover, the specification fails to describe other identifying characteristic of the claimed genus of nucleic acids that has the recited structure and function. In other words, the specification fails to describe a nexus between the claimed structure and the function of increasing protein production in any system. The nucleic acid sequences having 90% homology with SEQ ID NO: 25 are not sufficiently described because the specification fails to ascribe the protein production enhancing activity to any portion or variant of SEQ ID NO: 25. As such, whether sequences having 90% homology with SEQ ID NO: 5 have the claimed function is unpredictable. Although the art recognizes that the MARs having transcription activity generally has a wider minor groove and deeper major groove and a low melting temperature, the exact value for such parameters possessed by a nucleic acid molecule that has protein increasing activity is not precisely determined even years after the application is filed. The application also fails to describe such parameter for the claimed genus of nucleic acids that alleged to have protein production increasing activity. With regard to nucleic acids having 90% homology with SEQ ID NO: 25, having a melting temperature of between 55 and 75° and a DNA bending value of 4 radial degrees, wherein said bent DNA element comprises at least five contiguous AT or TA nucleotides and wherein said binding protein is a transcription factor, it is not sufficiently described because the specification does not describe which fragment, and or what type of variant of this DNA molecule have the protein producing increasing activity. Lastly, since the claimed DNA is not sufficiently described, the vector and host cell comprise said DNA

Art Unit: 1636

also lack description for same reason as set above. Thus, the specification fails to describe the invention in such a way to convey a skilled artisan that the inventors had possession of the invention at the time the application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 125 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new ground of rejection necessitated by amendment.**

Claim 125 recites the limitation "a sequence containing a promoter" in line 2. There is insufficient antecedent basis for this limitation in the claim because none of the parent claims recite a promoter.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

Art Unit: 1636

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 9:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636

